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SYNTHESIS OF (±)-1-DESOXY-2-LYCORINONE

AND OF A POSSIBLE *TRANS*-DIHYDRO-LYCORICIDINE PRECURSOR

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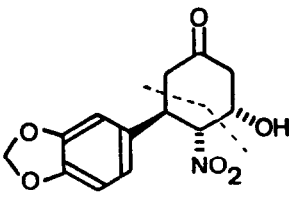
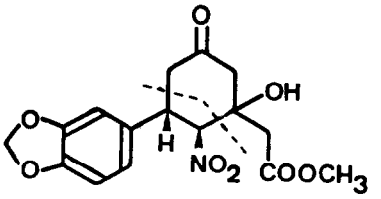
Summary: En-route from the 5-aryl-3-hydroxy-4-nitro-cyclohexanones 1 and 2, readily available from poly-enolates and 3.4-methylenedioxy-ω-nitro-styrene, to dihydro-lycoricidine 3 and to lycorine 4, respectively, the title compounds 9 and 14 are prepared in few steps.

As described in a previous paper[2], *Michael*-addition of doubly deprotonated acetyl acetaldehyde and of triply deprotonated methyl dioxo-hexanoate[3] to 1-methylenedioxyphenyl-2-nitro-ethene with appropriate workup leads to the diastereomerically pure, crystalline cyclohexanones 1 and 2, respectively. Inspection of the *formulae* of these compounds reveals that introduction of only one additional carbon atom should furnish the skeleton present in *trans*-dihydro-lycoricidine[4a] (3) and in lycorine[4b] (4). The present paper reveals that the functionality pattern of the intermediates involved renders this seemingly simple transformation a difficult task.



1



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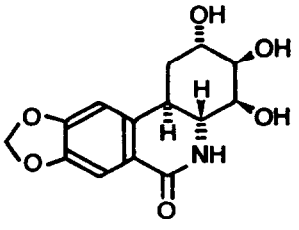

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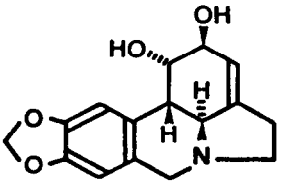
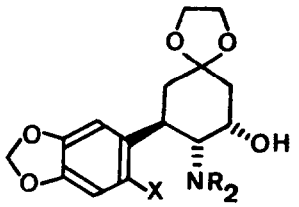


4

For the construction of the B/C-*trans*-fused phenanthridine derivative 9, the keto group of 1 was protected by conversion to the acetal 5 (82%), and the nitro group was reduced over *Raney*-nickel to give the aminoalcohol 6 (79%). All attempts to cyclize this compound with formation of the B-ring by conventional methods[5] have failed so far. We therefore turned to the Pd-catalyzed CO-insertion starting from ortho-bromo-phenethylamines[6]: bromination of 6 in the presence of acid gave the aryl bromide 7 (77%) which yielded the hydroxy-imine 8 (87%)

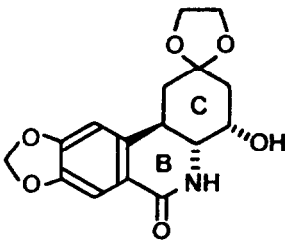


5 : X = H, R = O

6 : X = R = H

7 : X = Br, R = H

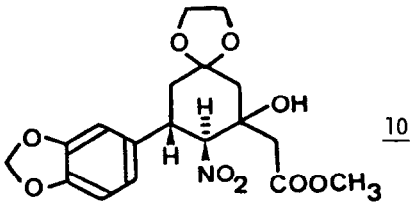
8 : X = Br, R = CHC_6H_5



9

upon treatment with benzaldehyde[7]. The carbonylation of 8 produced the B-ring-closed product 9 in a very slow conversion (20% after 30 h; 50% recovery of 8); for the reaction conditions and some properties of the compounds 5 - 9 see the accompanying table.

The elaboration of the two missing rings of the lycorine system from 2 took the following steps, also outlined with some product data in the table: acetalization to 10 and hydrogenation of the nitro-group[8a] as above, with subsequent heating in boiling xylene for lactam formation[8b] gave a *ca.* 60% overall yield of 11 which was reduced with lithium alanate to the aminoalcohol 12 (55%). Numerous attempts to cyclize this compound by one of the *Pictet-Spengler* recipes led to complex mixtures of products[9]. Only after acetal hydrolysis and dehydration to the very unstable enone 13, which was immediately treated with formaldehyde, did



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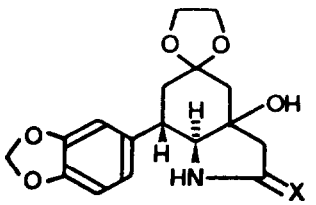
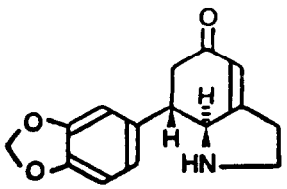


11 : X = O

12 : X = H/H



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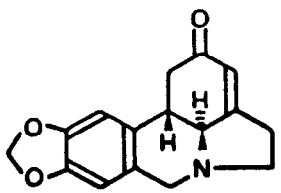

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Table. Reaction conditions for the transformations leading to 5 - 14. All new compounds gave correct elemental analyses and showed spectra fully compatible with the structures drawn. Only selected, characteristic data are listed here. The yields are given in the text. If not stated otherwise, crystallizations were carried out in CH_2Cl_2/hexane mixtures.

5	from 1, 2.5 equiv. ethylene glycol, a trace of TosOH, 60 min reflux in benzene with separation of water; m.p. 170-172°C; IR (KBr): 3480, 1556 cm^{-1}.
6	from 5, neutral *Raney*-Ni, ethanol, 30 bar H_2-pressure, 50°C, 17 h in a stainless steel autoclave; m.p. 116-117°C; IR (KBr): 3455, 3365, 3330, 3245 cm^{-1}.
7	from 6, 1.0 equiv. Br_2, in H_2O, 30 min at 0°C, in the presence of 1 equiv. of oxalic acid; m.p. 144-145°C; ^{1}H-NMR ($CDCl_3$): 6.99 (*s*) and 6.70 (*br. s*), 2 arom. H, 2.75 (*dxd*, *J*=2.5 and 11 Hz after addition of D_2O, H-C-N).
8	from 7, 1.2 equiv. benzaldehyde, trace of I_2, C_6H_6, 8 h, water separator; m.p. 174-175°C; IR (KBr): 3510, 1639 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 7.91 (*br. s*, H-C=N).
9	from 8, CO-atmosphere, 4 mole % $Pd(OAc)_2$, 6 mole % $P(C_6H_5)_3$, NEt_3/CH_3OH 10:3, 29 h, reflux, workup with 10% HOAc; m.p. (dec.) 242-245°C (from acetone/CH_2Cl_2); ^{1}H-NMR (300 MHz, DMSO-d_6, 100°C): 3.30 (*dxd*, *J*=2.5, 12.5 Hz, H-C-N); ^{13}C-NMR (DMSO-d_6): 164.0, 150.5, 145.9, 137.0, 122.9, 107.8 (six singlets), 106.8 (*d*), 104.6 (*d*), 101.4 (*t*), 65.7 (*d*), 64.2 (*t*), 63.1 (*t*), 57.7 (*d*), 38.4 (*t*), 35.9 (*t*), 32.0 (*d*).
10	83% from 2, as above for 1 → 5; m.p. 195-197°C; IR (KBr): 3495, 1731, 1556 cm^{-1}; ^{1}H-NMR (CD_3CN): 5.16 (*d*, *J*=12 Hz, H-C-NO_2).
11	from the crude product of hydrogenation of 10[8], xylene, 4d, 160°C; m.p. 244-246°C; IR (KBr): 3520 and 1692 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 3.42 (*d*, *J*=12 Hz, H-C-N).
12	from 11, 10 equiv. LAH, THF, 16 h, 50°C under argon; m.p. 164-166°C (sublimation 120°C/0.005 Torr).
13	from 12, 2 M HCl, 5.5 h, 50°C under argon; very unstable compound; heavy losses during chromatography (SiO_2, $CHCl_3/CH_3OH$ 25:1); crude product used for next step; IR ($CHCl_3$): 1660 cm^{-1}; ^{1}H-NMR ($CDCl_3$, trace of D_2O): 3.74 (*dxd*, *br.*, *J*=2 and 10.5 Hz, H-C (7a)); MS: 257 (M^+), 109 (basis peak, retro-*Diels-Alder* fragment).
14	from 13, 40% formalin, 2 M HCl, CH_3OH, 15 h, 50°C under argon; chromatography on Al_2O_3 (neutral) with Et_2O/toluene 5:2; m.p. 163-165°C (acetone) [ref. [10,12]) 159-161°C]; IR (KBr) 1655 cm^{-1}; UV [CH_3OH, λ_{max}(lgε)]: 229 (4.17), 293 nm (3.63); ^{13}C-NMR ($CDCl_3$): 198.7, 167.8, 146.6, 146.5, 129.6, 128.2 (six singlets), 122.3 (*d*), 107.2 (*d*), 105.0 (*d*), 101.1 (*t*), 67.4 (*d*), 56.3 (*t*), 53.3 (*t*), 40.6 (*d*), 40.1 (*t*), 29.8 (*t*).

we isolate the desired pentacyclic derivative 14 in poor yield (10%). Variation of the reaction conditions did so far not raise the yield[11]. Improvements of the cyclization steps (8 → 9 and 12 → 14) and further transformations are being actively investigated.

The present approach to the syntheses of the skeletons of lycorine and lycoricidine might well turn out to be one of the most attractive ones.

REFERENCES AND FOOTNOTES

1) Part of the dissertation (ETH No. 6916) of *Th. W.*, 1981.

2) *V. Ehrig, D. Seebach,* Chem. Ber. *108*, 1961 (1975).

3) *J.S. Hubbard, T.M. Harris,* J. Org. Chem. *46*, 2566 (1981).

4) For syntheses of the skeleton (a) of 3 see: *S. Ohta, S. Kimoto,* Chem. Pharm. Bull. *24*, 2977 (1976); *A. Mondon, K. Krohn,* Chem. Ber. *109*, 855 (1976); *K. Isobe, J. Taga, Y. Tsuda,* Heterocycles *9*, 625 (1978); *G.E. Keck, E. Boden, U. Sonnewald,* Tetrahedron Lett. *1981*, 2615; and (b) of 4 see: *S.F. Martin, C. Tu,* J. Org. Chem. *46*, 3763 (1981); and references cited in these papers.

5) *I.e.* by electrophilic aromatic substitution of the *Bischler-Napieralsky* and *Pictet-Spengler* type, as applied to a variety of derivatives of 6.

6) A general method of preparing benzolactams: *M. Mori, K. Chiba, Y. Ban,* J. Org. Chem. *43*, 1684 (1978); *K.P. Tiwari* et al., Synth. Commun. *10*, 523, 541 (1980), Tetrahedron *37*, 1213 (1981).

7) 8 showed no tendency to undergo the expected cyclization to an oxazolidine. - Direct Pd-catalyzed carbonylation of 7 led to the isolation of *ca.* 20% of the cyclic carbamate [m.p. 204-205°C (CH_2Cl_2/hexane); IR (KBr): 3430, 1748 cm^{-1}], *i.e.* the insertion product of CO into the NH and OH bonds without loss of the bromine atom.

8) (a) The product of hydrogenation consisted of a mixture of the aminoester [10, NH_2 instead of NO_2, m.p. 109°C (CH_2Cl_2/hexane); IR (KBr): 3490, 3360, 1737 cm^{-1}] and 11, ratio 6:1, total yield 90%. - (b) The crude mixture was heated without purification. The drastic conditions of lactam formation may be due to a *trans*-configuration of the amino and the carbomethoxy-methyl groups, cf. 1 and *M.S. Newman, C.A. Vander Werf,* J. Am. Chem. Soc. *67*, 233 (1945).

9) We had hoped that acid catalyzed deacetalization and dehydration to 14 would occur concomitantly with the cyclization, cf. ref. [10].

10) *H. Muxfeldt, J.P. Bell, J.A. Baker, U. Cuntze,* Tetrahedron Lett. *1973*, 4587.

11) A recently published aprotic modification of the *Pictet-Spengler* reaction [*G.E. Keck, R.R. Webb, II,* J. Am. Chem. Soc. *103*, 3173 (1981)] was not applied to 12 or 13, as yet. Also, the carbonylation (cf. 8 → 9) was not yet tested for the lycorine skeleton.

12) Cf. also: *K. Kotera,* Tetrahedron *12*, 240 (1961).

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